

Clinical implication of gastrointestinal bleeding in degenerative aortic stenosis: An update

Wojciech Gola, Małgorzata Lelonek

Department of Cardiology, Sterling Memorial University Hospital, Medical University of Lodz, Poland

Abstract

Gastrointestinal (GI) bleeding due to colonic angiodysplasias can be associated with calcifying aortic stenosis (AS). GI angiodysplasias and AS are defined as chronic degenerative disorders, and the prevalence of both diseases increases with age. Moreover, degenerative AS is associated with increased destruction of high molecular weight multimers of von Willebrand factor which can promote bleeding from intestinal angiodysplasias. The coincidence of gastrointestinal bleeding angiodysplasias and AS has been known for many years as Heyde's syndrome. Aortic valve replacement is the first line therapy for advanced stage AS-patients, but can also be an effective treatment for co-existent bleeding angiodysplasias and acquired von Willebrand disease.

In this study, we tried to collect as well as systemized data about the etiopathogenesis of AS coagulation abnormalities and diagnostic, clinical and therapeutic implications of AS-patient with GI angiodysplasias. (Cardiol J 2010; 17, 4: 330–334)

Key words: aortic stenosis, angiodysplasia, von Willebrand disease, Heyde's syndrome

Introduction

Aortic stenosis (AS) can be complicated by coagulation abnormalities. The commonest and best documented clinical manifestation is hemorrhagic tendency, such as gastrointestinal (GI) [1, 2] and nasal bleeding [3, 4]. Bleeding from the GI system usually occurs in elderly patients with co-existent GI angiodysplasias. An association between AS and GI bleeding was first suggested in 1958 by Edward J. Heyde, an internist working in Vancouver. He noted (in a letter to the *New England Journal of Medicine*) ten cases of coincidence between calcifying AS and GI bleeding of obscure origin [5]. GI bleeding angiodysplasia with co-existent autopsy-proven AS was first corroborated in 1971 by Boss and Rosenblum [6]. The hypothesis of association between degenerative AS and GI bleeding due to colonic angiodysplasia was confirmed by further studies and has been termed Heyde's syndrome

(HS). Warkentin et al. [7] suggested that GI bleeding angiodysplasia in AS-patients is caused by acquired type 2A von Willebrand disease (vWD-2A), characterized by decreased level of high molecular weight (HMW) von Willebrand factor (vWF) multimers. Recent research confirmed this etiology of the HS phenomenon (Fig. 1) [7–9].

Prevalence

AS is the commonest valvular heart defect and affects 3–5% of the population aged 65 and over [10, 11]. But, the prevalence of AS in patients with bleeding from colonic angiodysplasia is still undefined and controversial. The incidence of GI bleeding in the general population is about 0.9% [12]. According to different sources, between 7–29% [13, 14] of patients with diagnosed GI bleeding angiodysplasias suffer from AS or aortic sclerosis, and 3% of advanced AS-patients have GI bleeding [12].

Address for correspondence: Wojciech Gola, Department of Cardiology, Sterling Memorial University Hospital, Medical University of Lodz, Sterlinga 1/3, 91–425 Łódź, Poland, e-mail: golawojtek@gmail.com

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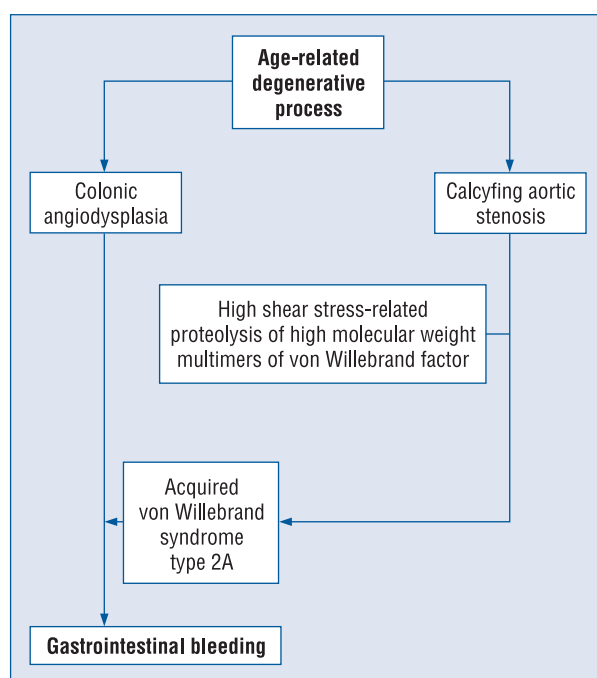


Figure 1. Pathogenesis of Heyde's syndrome.

On the other hand, one study showed no relation between AS and GI bleeding [15].

Association between degenerative aortic stenosis and von Willebrand disease

Von Willebrand factor

Von Willebrand factor (vWF) is a multimeric glycoprotein (20,000 kD) that circulates in blood plasma and binds to coagulation factor VIII in a non-covalent complex. vWF is produced constitutively in endothelium (in the Weibel-Palade bodies), megakaryocytes (α -granules of platelets), and sub-endothelial connective tissue. vWF plays a role in primary hemostasis and helps in the proper adhesion of platelets to the exposed subendothelium due to damage occurring to the blood vessels [16]. In forming thrombus, and during normal wear, large multimers of vWF are cut by plasma vWF-cleaved metalloprotease called ADAMTS 13 (a disintegrin and metalloprotease with thrombospondin type 1 motifs) [17].

Acquired type 2A von Willebrand disease as a consequence of high shear stress

In AS-patients, HMW von Willebrand factor multimers, normally circulating in plasma, are subject to high fluid shear stress presented in narrowed aortic valve [18]. During passing stenotic

Table 1. Commonest disorders causing von Willebrand syndrome type 2A [9, 22–25].

Degenerative aortic stenosis	
Hypertrophic cardiomyopathy with left ventricular outflow tract obstruction	} Cardiovascular diseases
Ventricular septal defect	
Patent ductus arteriosus	
Immunologic disorders (systemic lupus erythematosus, scleroderma, mixed connective tissue disease, diabetes mellitus)	
Acute leukemia and non-hematologic neoplasms	
Drugs (hydroxyethyl starch, ciprofloxacin, griseofulvin, valproic acid, recombinant factor VIII)	
Monoclonal gammopathies	
Uremia	
Renal insufficiency	
Cirrhosis of the liver	
Pulmonary hypertension	

aortic valve, under conditions of high shear stress, large multimers of vWF are subject to increased exposure of ADAMTS 13 [19, 20]. High shear stress changes the structure of vWF and makes it more prone to proteolysis. The effect of increased vWF proteolysis is depletion of HMW multimers that are the most hemostatically important in primary hemostasis. There is significant dependence between numbers of HMW multimers and aortic valve gradient (AVG) [21]. Decreased number of HMW von Willebrand multimers is a laboratory manifestation of acquired vWD-2A.

Acquired depletion of HMW multimers, also called von Willebrand syndrome type 2A (vWS-2A), can be a result of many other disorders. The commonest reasons for vWS-2A are shown in Table 1.

Laboratory manifestations of vWS-2A

Loss of HMW vWF multimers is a basic laboratory manifestation of acquired vWD-2A in patients suffering from AS. Electrophoretic analysis of vWF multimers is the method of choice [26]. Prolonged bleeding time, decreased ristocetin co-factor activity (vWF:RCo), and decreased vWF antigen (vWF:Ag) are also common laboratory symptoms of vWD-2A and can be useful in the diagnostic process [27]. Moreover, a lower level of vWF:RCo than vWF:Ag is characteristic for most patients with vWD-2A [27]. However, partial thromboplastin time is usually normal and factor VIII level is often not lowered [26]. HMW multimers are markedly lowered even in subtle form of vWD-2A with normal results of skin bleeding time, vWF:RCo and vWF:Ag [27].

Aortic stenosis and angiodysplasia

Angiodysplasia is a mucosal and submucosal vascular malformation that occurs typically in a colon. Histologically, it is similar to teleangiectasia and is formed by enlarged and fragile vessels. The typical location for angiodysplastic changes is the right side of the colon (cecum and ascending colon) but it can also occur in the stomach and the small intestine [28]. Other locations of bleeding angiodysplasias like nasal mucosa have also been described [4]. Colonic angiodysplasia can be found in 1–6% of patients admitted to the hospital with GI bleeding symptoms [29, 30]. Depletion of HMW multimers of vWF in AS (vWS-2A) increases risk of bleeding from co-existent angiodysplasia [7, 22].

Degenerative process as a causative factor of angiodysplasia and aortic stenosis

The degenerative age-related process plays a major role in forming GI angiodysplasia [31]. The same process is a main etiology of calcifying AS (degenerative AS, age-related AS) [32] and connects these two disorders. Angiodysplasia and degenerative AS typically appear in advanced age.

Hypoxemic theory

Narrowed aortic valve decreases perfusion in the GI tract, causes hypoxemia and is the main reason for persistent vasodilatation in GI mucosa. Permanent dilatation of GI vessels promotes intestinal angiodysplasias [33].

Genetic predisposition

Other factors like genetic predisposition may also result in colonic angiodysplasias and calcifying AS [31]. Congenital connective tissue disorders can intensify the degenerative process in colonic connective tissue and accelerate the age-related degeneration process in the aortic valve (congenital bicuspid aortic valve) [34].

Investigation for angiodysplasia

The investigation of intestinal angiodysplasia is still imperfect because malformed vessels may sometimes be very tiny and impossible to detect, hence some patients may be under-diagnosed. However, selective angiography of mesenteric arteries is recommended as a 'gold standard' (Fig. 2) [29]. One limitation of this procedure is that it has to be performed during an episode of bleeding, otherwise it is not reliable. Angiodysplastic lesions can also be identified via colonoscopy (Fig. 3) but some patients with GI bleeding who are diagnosed with angiodysplasia show a normal result to this procedure

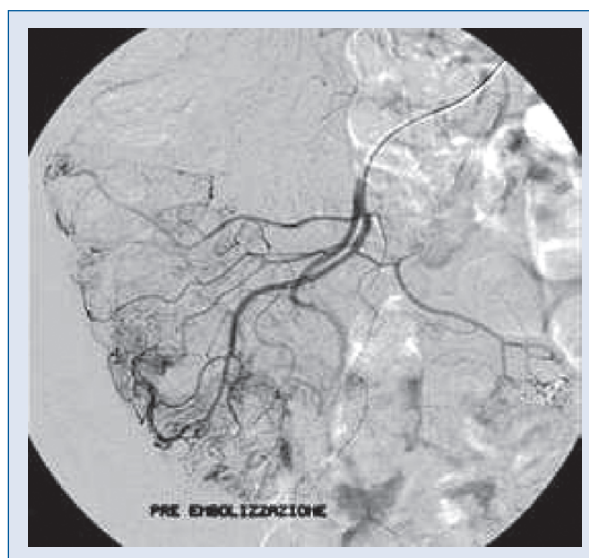


Figure 2. Selective angiography of superior mesenteric artery. Multiple areas of small angiodysplasias localized at cecum and ascending colon (<http://www.eurorad.org/eurorad/case.php?id=7814>).

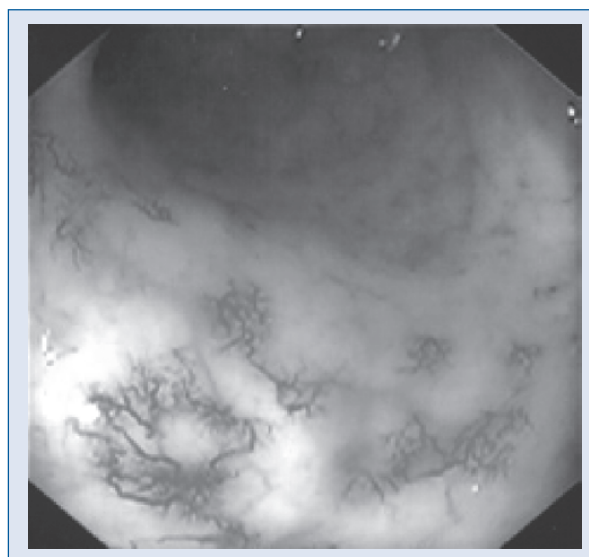


Figure 3. Colonoscopic view of gastrointestinal angiodysplasias (<http://www.gihealth.com/html/education/photo/colonAngiodysplasia.html>).

[28, 29, 35]. Other investigations that can help diagnose angiodysplasia include capsule enteroscopy and double-balloon enteroscopy, both of these facilitate visualization of the small intestine [36], labeled red blood cell scintigraphy and endoscopic Doppler sonography.

Management of Heyde's syndrome

Aortic valve replacement as a treatment of choice

There are many methods of HS therapy. However, aortic valve replacement (AVR) should be recommended as a 'gold standard' [37, 38]. It is proven that AVR corrects the blood supply in the gut. Moreover, decreased number of HMV vWF multimers undergoes normalization after valve replacement [39]. It is reported that 95% of AS-patients with GI bleeding due to angiodysplasia have no bleeding symptoms after AVR [40]. Replacement with biologic prosthesis is recommended as the first line treatment for AS-patients with co-existent gastrointestinal bleeding [41]. Patients with a replaced mechanical valve should take anticoagulants, which would increase angiodysplasias bleeding [42].

Other treatment options for angiodysplasia

Another (though less effective) management method for GI angiodysplasia is endoscopy including laser photocoagulation, sclerotherapy and electrocoagulation [43]. Selective embolization during mesenteric angiography can be useful in patients with severe bleeding lesions and can be an alternative to surgical treatment [44, 45]. Laparotomy and gastrointestinal surgery in the form of segmental bowel resection or blind right colectomy is recommended in some cases [46]. There have been positive reports of systemic treatment in GI bleeding angiodysplasia. Hormonal therapy including small doses of ethinyl estradiol [47], progesterone, somastatin [48] and long-acting octreotide [49] can help control bleeding. Thalidomide, oral iron, antifibrinolytics, and vWF/factor VII (FVIII) concentrate [45, 50] have also been reported as treatment methods for GI angiodysplasias.

Conclusions

Calcifying aortic stenosis can be complicated by GI bleeding which is linked to colonic angiodysplasia. Co-existent type-2A von Willebrand syndrome in AS-patients promotes hemorrhagic tendency from angiodysplasias. Both of these disorders, calcifying AS and angiodysplasias, appear in elderly patients and are promoted by age-related degenerative process. Episodes of GI bleeding may become dangerous and problematic, especially in elderly patients, and may complicate the diagnostic and therapeutic process. It is very important to know that HS in the form of both its components can be efficiently cured by one valve replacement therapy.

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References

1. King RM, Pluth JR, Giuliani ER. The association of unexplained gastrointestinal bleeding with calcific aortic stenosis. *Ann Thorac Surg*, 1987; 44: 514–516.
2. Olearchyk AS. Heyde's syndrome. *J Thorac Cardiovasc Surg*, 1992; 103: 823–824.
3. Preik M, Strauer BE. Recurrent epistaxis in a patient with aortic valve stenosis: A variant of Heyde syndrome? *Med Klin (Munich)*, 2002; 15: 97: 170–173.
4. Schödel J, Obergfell A, Maass AH. Severe aortic valve stenosis and nosebleed. *Int J Cardiol*, 2007; 120: 286–287.
5. Heyde EC. Gastrointestinal bleeding in aortic stenosis. *N Engl J Med*, 1958; 259: 196.
6. Boss EG, Rosenblum JM. Bleeding from the right colon associated with aortic stenosis. *Am J Dig Dis*, 1971; 16: 269–275.
7. Warkentin TE, Moore JC, Morgan DG. Aortic stenosis and bleeding gastrointestinal angiodysplasia: Is acquired von Willebrand's disease the link? *Lancet*, 1992; 340: 35–37.
8. Vincentelli A, Susen S, Le Tourneau T et al. Acquired von Willebrand syndrome in aortic stenosis. *N Engl J Med*, 2003; 349: 343–349.
9. Warkentin TE, Moore JC, Anand SS, Lonn EM, Morgan DG. Gastrointestinal bleeding, angiodysplasia, cardiovascular disease, and acquired von Willebrand syndrome. *Transfus Med Rev*, 2003; 17: 272–286.
10. Vahanian A, Baumgartner H, Bax J et al. Guidelines on the management of valvular heart disease. The Task Force of Management of Valvular Heart Disease of the European Society of Cardiology. *Eur Heart J*, 2007; 28: 239–243.
11. O'Brien KD, Reichenbach DD, Marcovina SM, Kuusisto J, Alpers CE, Otto CM. Apolipoproteins B, (a), and E accumulate in morphologically early lesion of "degenerative" valvular aortic stenosis. *Arterioscler Thromb Vasc Biol*, 1996; 16: 523–532.
12. Pate GE, Mulligan A. An epidemiological study of Heyde's syndrome: An association between aortic stenosis and gastrointestinal bleeding. *J Heart Valve Dis*, 2004; 13: 713–716.
13. Mishra PK, Kovac J, Caestecker J, Fancourt G, Logtens E, Spyt T. Intestinal angiodysplasia and aortic valve stenosis: Let's not close the book on this association. *Eur J Cardiothorac Surg*, 2009; 35: 628–634.
14. Shoenfeld Y, Eldar M, Bedazovsky M. Aortic stenosis associated with gastrointestinal bleeding. A survey of 612 patients. *Am Heart J*, 1980; 100: 179–182.
15. Imperiale TF, Ransohoff DF. Aortic stenosis, idiopathic gastrointestinal bleeding, and angiodysplasia: Is there an association? A methodologic critique of the literature. *Gastroenterology*, 1988; 95: 1670–1676.
16. Sadler JE. Biochemistry and genetics of von Willebrand factor. *Annu Rev Biochem*, 1998; 67: 395–424.
17. Zheng X, Chung D, Takayama TK et al. Structure of von Willebrand factor cleaving protease (ADAMTS13), a metalloprotease involved in thrombotic thrombocytopenic purpura. *J Biol Chem*, 2001; 276: 41059–41063.

18. Tsai HM, Sussman II, Nagel RL. Shear stress enhances the proteolysis of von Willebrand factor in normal plasma. *Blood*, 1994; 83: 2171–2179.
19. Pareti FI, Lattuada A, Bressi C. Proteolysis of von Willebrand factor and shear stress-induced platelet aggregation in patients with aortic valve stenosis. *Circulation*, 2000; 102: 1290–1295.
20. Sadler JE. Aortic stenosis, von Willebrand factor, and bleeding. *N Engl J Med*, 2003; 349: 323–325.
21. Tsai HM. Shear stress and von Willebrand factor in health and disease. *Semin Thromb Hemost*, 2003; 29: 479–488.
22. Fressinaud E, Meyer D. International survey of patients with von Willebrand disease and angiodysplasia. *Thromb Haemost*, 1993; 70: 546.
23. Fujita H, Tomiyama J, Chuganji Y et al. Diffuse angiodysplasia of the upper gastrointestinal tract in a patient with hypertrophic obstructive cardiomyopathy. *Intern Med*, 2000; 39: 385–388.
24. Tatebe S, Kanazawa H, Yamazaki Y et al. Closure of a ventricular septal defect in a patient with von Willebrand disease. *Surg Today*, 1997; 27: 661–663.
25. Rauch R, Budde U, Girsch M et al. Acquired von Willebrand disease in an infant. Resolution by interventional occlusion of patent ductus arteriosus. *Thromb Res*, 2001; 102: 407–409.
26. Veyradier A, Fressinaud E, Meyer D. Laboratory diagnosis of von Willebrand disease. *Int J Clin Lab Res*, 1998; 28: 201–210.
27. Meyer D, Fressinaud E, Hilbert L, Ribba AS, Lavergne JM, Mazurier C. Type 2 von Willebrand disease causing defective von Willebrand factor-dependent platelet function. *Best Pract Res Clin Haematol*, 2001; 14: 349–364.
28. Höchter W, Weingart J, Kuhner W et al. Angiodysplasia in the colon and rectum. Endoscopic morphology, localisation and frequency. *Endoscopy*, 1985; 17: 182–185.
29. Foutch PG. Angiodysplasia of the gastrointestinal tract. *Am J Gastroenterol*, 1993; 88: 807–818.
30. Heer M, Sulser H, Hany A. Angiodysplasia of the colon: An expression of occlusive vascular disease. *Hepatogastroenterology*, 1987; 34: 127–131.
31. Sucker C. The Heyde syndrome: Proposal for a unifying concept explaining the association of aortic valve stenosis, gastrointestinal angiodysplasia and bleeding. *Int J Cardiol*, 2007; 115: 77–78.
32. Lindross M, Kupari M, Heikkilä J, Tilvis R. Prevalences of aortic valve abnormalities in the elderly: an echocardiographic study of a random population sample. *J Am Coll Cardiol*, 1993; 21: 1220–1225.
33. Boley SJ, Sammartano R, Adams A, DiBiase A, Kleinhaus S, Sprayregen S. On the nature and etiology of vascular ectasias of the colon. *Gastroenterology*, 1977; 72: 650–660.
34. Lewin MB, Otto CM. The bicuspid aortic valve: adverse outcomes from infancy to old age. *Circulation*, 2005; 111: 832–834.
35. Clouse RE, Costigan DJ, Mills BA et al. Angiodysplasia as a cause of upper gastrointestinal bleeding. *Arch Intern Med*, 1985; 145: 458–461.
36. Kameda N, Higuchi K, Shiba M et al. A prospective, single-blind trial comparing wireless capsule endoscopy and double-balloon enteroscopy in patients with obscure gastrointestinal bleeding. *J Gastroenterol*, 2008; 43: 434–440.
37. Anderson RP, McGrath K, Street A. Reversal of aortic stenosis, bleeding gastrointestinal angiodysplasia, and von Willebrand syndrome by aortic valve replacement. *Lancet*, 1996; 347: 689–890.
38. Cappell MS, Lebowitz O. Cessation of recurrent bleeding from gastrointestinal angiodysplasias after aortic valve replacement. *Ann Intern Med*, 1986; 105: 54–57.
39. Valen G, Blombäck M, Sellei P et al. Release of von Willebrand factor by cardiopulmonary bypass, but not by cardioplegia in open heart surgery. *Thromb Res*, 1994; 73: 21–29.
40. Love JW. The syndrome of calcific aortic stenosis and gastrointestinal bleeding: resolution following aortic valve replacement. *J Thorac Cardiovasc Surg*, 1982; 83: 779–783.
41. Apostolakis E, Doering C, Kantartzis M, Winter J, Schulte HD. Calcific aortic-valve stenosis and angiodysplasia of the colon: Heyde's syndrome-report of two cases. *Thorac Cardiovasc Surg*, 1990; 38: 374–376.
42. Baciewicz Jr FA, Davis JT. Heyde's syndrome: Failure of a mechanical prosthesis and the possibility of a coagulation defect. *Ann Thorac Surg*, 1987; 44: 554–555.
43. Singh P, Scoyni R, Pooran N et al. Aortic valve replacement: A last resort for aortic stenosis-associated refractory GI bleeding. *Gastrointest Endosc*, 2002; 56: 139–141.
44. Funaki B, Kostelic JK, Lorenz J et al. Superselective microcoil embolization of colonic hemorrhage. *AJR Am J Roentgenol*, 2001; 177: 829–836.
45. Floudas CS, Moyssakis I, Pappas P, Gialafos EJ, Aessopos A. Obscure gastrointestinal bleeding and calcific aortic stenosis (Heyde's syndrome). *Int J Cardiol*, 2008; 127: 292–294.
46. Warkentin TE, Moore JC, Anand SS, Lonn EM, Morgan DG. Gastrointestinal bleeding, angiodysplasia, cardiovascular disease, and acquired von Willebrand syndrome. *Transfus Med Rev*, 2003; 17: 272–286.
47. Granieri R, Mazzulla JP, Yarborough GW. Estrogen-progestone therapy for recurrent gastrointestinal bleeding secondary to gastrointestinal angiodysplasia. *Am J Gastroenterol*, 1988; 83: 556–558.
48. Andersen MR, Aaseby J. Somatostatin in the treatment of gastrointestinal bleeding caused by angiodysplasia. *Scand J Gastroenterol*, 1996; 31: 1037–1039.
49. Bowers M, McNulty M, Mayne E. Octreotide in the treatment of gastrointestinal bleeding caused by angiodysplasia in two patients with von Willebrand's disease. *Br J Haematol*, 2000; 108: 524–527.
50. Bounds BC, Friedman LS. Lower gastrointestinal bleeding. *Gastroenterol Clin North Am*, 2003; 32: 1107–1125.